REMARKS

This communication is being filed in response to the Office Action dated October 16, 2003. Claims 1-3, 5-11 and 15-17 are pending. Claims 11, 16 and 17 are amended as described herein to correct certain informalities. Claims 11 and 17 have been amended to insert the term "and" after the penultimate member of the Markush group. Claims 16 and 17 have been amended to correct the numbers of the claims from which they depend.

Claims 1-2 and 5-11 are rejected under the first paragraph of 35 U.S.C. § 112, because, according to the Examiner, the specification does not enable any person skilled in the art to which the invention pertains, or with which it is most nearly connected, to make and use the invention commensurate with the scope of these claims.

Claims 1-3, 5-11 and 15-17 are rejected under 35 U.S.C. § 103(a) as being rendered obvious by Max *et al.* (Int. J. Cancer 1997;71:320-324) in view of Taylor *et al.* (Taylor *et al.*, Blood 1997;89:4078-4084), Mohle *et al.* (Proc. Natl. Acad. Sci. USA 1997;94:663-668) and Charo *et al.* (J. Biol. Chem. 1987;262:9935-9938) as evidenced by Coller *et al.* (Haemostasis 1996;26:285-293).

Applicants respectfully traverse the Examiner's rejections of the aforementioned claims for the reasons set forth below.

I. The Claims are Enabled under the first paragraph of 35 U.S.C. § 112

Claims 1-2 and 5-11 are rejected under the first paragraph of 35 U.S.C. § 112 because, according to the Examiner, the specification does not enable any person skilled in the art to which the invention pertains, or with which it is most nearly connected, to make and use the invention commensurate with the scope of these claims. Specifically, the Examiner contends that the claims are still broadly drawn to a method for inhibiting angiogenesis in a mammal comprising administering a monoclonal antibody or fragment thereof which acts as an antagonist of the integrins

$\alpha_v\beta_3$ and GPIIb/IIIa ($\alpha_{IIb}\beta_3$).

Applicants have previously argued that methods for identifying molecules that bind to and antagonize these integrin molecules were well-known in the art at the time of the instant invention, and that there is no evidence to suggest that 7E3 is the only possible antibody with the claimed properties. The Examiner concedes that the screening procedures are routine, but still maintains that such routine screens would not be able to identify antibodies other than 7E3 that have the claimed properties, namely the ability to antagonize $\alpha_v\beta_3$ and GPIIb/IIIa ($\alpha_{IIb}\beta_3$). The Examiner appears to base this conclusion on the observation by Reverter *et al.* (J. Clin. Invest. 1996;98:863-874) that the "combined inhibitory effect of 10E5 and LM609 did not *quite* equal that produced by 7E3 alone" (emphasis added).

In response, Applicants assert that the observation by Reverter *et al.* (*i.e.* that the combined application of 10E5, which binds to GPIIb/IIIa ($\alpha_{IIb}\beta_3$) but not to $\alpha_v\beta_3$, and LM609, which binds to $\alpha_v\beta_3$ but not GPIIb/IIIa ($\alpha_{IIb}\beta_3$), is less efficacious than the application of 7E3, which simultaneously and locally binds both $\alpha_v\beta_3$ and GPIIb/IIIa ($\alpha_{IIb}\beta_3$)), is relevant only to the desirability of identifying a single immunoglobulin molecule which possesses both properties, and does not suggest that the identification of such a molecule could not be achieved using methods that were routine in the art at the time of the instant invention. Applicants assert that the presence of both binding properties within 7E3 does not preclude their presence in other immunoglobulin molecules.

As for the Examiner's argument that "the specification has not demonstrated the reproducible production of antibodies which have properties identical to 7E3 and recited in claim 1[,]" Applicants respectfully submit that the Examiner is improperly reading an additional limitation into the claims, namely that the properties of the antibodies must be "identical" to those of 7E3.

Regarding whether "undue experimentation" would be required to identify antibodies other

than 7E3 having the recited integrin-binding properties, a majority of the factors enumerated in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986) as indicia of enablement are in fact satisfied in the instant case. The nature of the invention, relating to monoclonal antibodies of a certain specificity and their method of use, is well-defined and clearly set forth in the specification.

At the time of the instant invention, the state of the prior art also was well-developed; the generation of monoclonal antibodies through the use of hybridoma-based technologies could certainly be characterized as within the skill of the ordinary artisan in the field. Ample support for this statement may be drawn from several of the references listed in the Information Disclosure Statement filed on July 15, 2002, including U.S. Patent No. 5,440,020 to Coller *et al.*, in which the procedures used to isolate and characterize 7E3 were described in detail. Other disclosed references that demonstrate the level of skill at the time of the instant invention include U.S. Patent No. 5,753,230 to Brooks *et al.*, which teaches how to identify, without undue experimentation, a monoclonal antibody exhibiting the same specificity as a known monoclonal antibody (column 17), U.S. Patent No. 4,474,893 to Reading, which teaches the generation of monoclonal antibodies that recognize two or more antigens, and Sevier *et al.*, *Clin Chem* 1981;27:1797-1806, which defines monoclonal antibodies as reagents of choice for immunological studies based on their homogeneity, specificity and *availability*.

The level of skill of the ordinary artisan in the field of the instant invention also could be characterized as high. Generally speaking, those who develop and characterize monoclonal antibodies hold doctorate degrees or their equivalent and have several years of intensive laboratory training in the field of immunology. Support for this statement may be found merely by examining the qualifications of the instant inventors and the inventors of other inventions relating to monoclonal antibodies, such as Drs. Brooks (U.S. No. 5,753,230) and Reading (U.S. No. 4,474,893),

both of whom hold doctoral degrees.

As for the level of predictability in the field, Applicants contend that the proper measure is not the ability to foresee what "specifically defined characteristics" the desired antibody will possess, but rather the predictable nature of the *process* utilized to generate monoclonal antibodies having a desired set of properties. As noted above, the predictability of the process of developing monoclonal antibodies specific for a given antigen was appreciated as early as 1981 (Sevier *et al.*, *Clin Chem* 1981;27:1797-1806).

In the instant case, the amount of direction is high, the specification having disclosed the exact method used to generate the 7E3 antibody, and one working example is explicitly taught.

The Examiner argues that undue experimentation would be required for one of ordinary skill in the art to practice the invention as claimed. However, Applicants contend that enablement is not precluded merely because some experimentation may be required. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986). Applicants respectfully submit that, owing to the routine nature of the screening processes as described above, and in light of the specific teachings of the instant specification regarding the methods employed to screen the monoclonal antibodies generated by these routine methods, the *quantity* of experimentation required would not rise to the level where it could be characterized as "undue." *See In re Wands*, 858 F.2d 731, 737.

Based on the fact that at least seven of the eight factors set forth in *Ex parte Forman* are satisfied in the instant case, Applicants assert that they are entitled to claims directed toward a single monoclonal antibody molecule that simultaneously antagonizes the integrins $\alpha_v\beta_3$ and GPIIb/IIIa ($\alpha_{IIb}\beta_3$), and methods of use thereof. Applicants therefore respectfully request the withdrawal of the rejection of Claims 1-2 and 5-11 under the first paragraph of 35 U.S.C. § 112 for lack of enablement.

II. The Claims are Not Obvious under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-3, 5-11 and 15-17 under 35 U.S.C. § 103(a) as being rendered obvious by Max *et al.* (Int. J. Cancer 1997;71:320-324) in view of Taylor *et al.* (Taylor *et al.*, Blood 1997;89:4078-4084), Mohle *et al.* (Proc. Natl. Acad. Sci. USA 1997;94:663-668) and Charo *et al.* (J. Biol. Chem. 1987;262:9935-9938) as evidenced by Coller *et al.* (Haemostasis 1996;26:285-293). The Examiner characterizes the teachings of each of these documents as follows: Max *et al.* teach expression of $\alpha_v\beta_3$ on tumor cells and cells involved in angiogenesis; that angiogenesis contributes to diabetic retinopathy; that an antibody to $\alpha_v\beta_3$ detected integrin in cells; and that tumors can be treated with $\alpha_v\beta_3$ antagonists. Taylor *et al.* teach the use of 7E3 and related molecules, in the claimed dosages and routes of administration, for protection of baboons against microangiopathic hemolytic anemia and microvascular thrombotic renal failure. Charo *et al.* teach that administration of 7E3 inhibits platelet aggregation by binding to GPIIb/IIIa ($\alpha_{IIb}\beta_3$). Mohle *et al.* teach that VEGF is produced from activated platelets, that VEGF is delivered to the site of injury by activated platelets, and that local secretion of VEGF may initiate angiogenesis. Thus, according to the Examiner, one of ordinary skill would be able to supplement the teachings of Max *et al.*, which the Examiner acknowledges do not teach intravenous administration of 7E3 to treat an inflammatory disease, with the other teachings cited above to cover the treatment of angiogenesis and related diseases.

In response, Applicants first would like to clarify several issues regarding the teachings of the prior art references. With regard to Max *et al.*, Applicants respectfully note that this report teaches that the integrin $\alpha_v\beta_3$ is expressed on endothelial cells present in the vasculature of various human epithelial tumors. Applicants also note that Max *et al.* further teach that $\alpha_v\beta_3$ is present, albeit at slightly lower levels, in vascular tissues of non-cancerous tissues and also in extravascular

cell types found in both normal and tumor specimens. In light of the observed distribution of $\alpha_v\beta_3$ on both endothelial and non-endothelial cell types in both normal and tumor samples, Applicants assert that Max *et al.* does not and cannot stand for the proposition that $\alpha_v\beta_3$ expression is important in neovascularization of tumors and hence their treatment by antagonists of $\alpha_v\beta_3$. In fact, Max *et al.*, on p. 323, concede that their results "show that $\alpha_v\beta_3$ expression is not limited to areas of neovascularization." Furthermore, in trying to explain their findings, Max *et al.*, on p. 324, suggest that "it is possible that $\alpha_v\beta_3$ expression on the normal vasculature does not serve any angiogenic function at all[!]" Thus, Applicants contend that one would be hard pressed to conclude from the findings of Max *et al.*, *or their interpretations of their own work*, that their study teaches a critical role for $\alpha_v\beta_3$ in either angiogenesis or tumor growth. This deficiency in their teaching is not remedied by those of Taylor *et al.*, Charo *et al.*, or Mohle *et al.*, since none of these works teach a role for $\alpha_v\beta_3$ in angiogenesis or tumor growth.

The Examiner also relies on Max *et al.* as teaching that "angiogenesis contributes to diabetic retinopathy" and that "tumors can be treated with $\alpha_v\beta_3$ antagonists[.]" Unfortunately, a careful reading of Max *et al.* reveals that neither of these propositions are actually taught by these authors. Rather, they are merely conclusory restatements of what the authors perceive to be the prior teachings of the field. Both comments appear in the introductory section of the report (p. 320). The statement regarding a potential role for angiogenesis in diabetic retinopathy is unsupported by a citation, while the assertion that tumors may be treated with $\alpha_v\beta_3$ antagonists is supported by citations to several papers by Brooks *et al.* (Science 1994;264:569-571; Cell 1994;79:1157-1164; and J. Clin. Invest. 199;96:1815-1822).

Applicants respectfully submit that this application of Max *et al.* largely a revisitation of the issues addressed in Applicants' previous response. For example, Applicants previously explained

the deficiencies of the work of Brooks *et al.* with regard to the use of monoclonal antibodies to inhibit both $\alpha_v\beta_3$ and GPIIb/IIIa ($\alpha_{IIb}\beta_3$). To briefly reiterate, the studies of Brooks *et al.* cited in Max *et al.* employ the monoclonal antibody LM609 to inhibit angiogenesis. Because LM609 antagonizes $\alpha_v\beta_3$, Brooks *et al.* focus only on the role of $\alpha_v\beta_3$ in angiogenesis, and do not recognize a potential role for GPIIb/IIIa ($\alpha_{IIb}\beta_3$)-mediated processes. This focus on only blockade of $\alpha_v\beta_3$ is reflected in their related U.S. patent, wherein (U.S. Patent No. 5,753,230; column 3, lines 22-25) it is stated that:

> [i]n a particularly preferred embodiment, the $\alpha_v\beta_3$ antagonist . . . does not substantially inhibit binding of fibrinogen to $\alpha_{IIb}\beta_3$.

Thus, Brooks *et al.* discourage the from the use of agents such as the 7E3 antibody of the instant invention that antagonize both $\alpha_v\beta_3$ and GPIIb/IIIa ($\alpha_{IIb}\beta_3$). Substituting the teachings of Max *et al.* for those of Brooks *et al.* therefore does not render obvious the use of 7E3 and related antibodies to treat proliferative and inflammatory diseases. Combining Max *et al.* with the other cited works cannot change the fact that the underlying observation in Max *et al.*, imported from the work of Brooks and colleagues, relates to the use of LM609, which lacks anti-GPIIb/IIIa ($\alpha_{IIb}\beta_3$), and not to the combined antagonism of both $\alpha_v\beta_3$ and GPIIb/IIIa ($\alpha_{IIb}\beta_3$), which is only taught by the instant invention.

Alternatively, the Examiner argues that it would have been obvious to the artisan of ordinary skill to extend the teachings of Taylor *et al.* to use the 7E3 antibody to treat proliferative and inflammatory disorders because of its antagonistic activities toward both $\alpha_v\beta_3$ and GPIIb/IIIa ($\alpha_{IIb}\beta_3$). According to the Examiner, 7E3's anti-$\alpha_v\beta_3$ properties would be useful because Max *et al.* teach that angiogenesis involves the $\alpha_v\beta_3$ integrin, that angiogenesis is involved in cancer and diabetic retinopathy, that antibodies to $\alpha_v\beta_3$ can be used as antagonists of $\alpha_v\beta_3$, and that $\alpha_v\beta_3$ is a target for

cancer and other diseases. The anti-GPIIb/IIIa ($\alpha_{IIb}\beta_3$) properties of 7E3 would be useful because, according to the Examiner, Taylor *et al.* teach that 7E3 inhibits platelet function by blocking GPIIb/IIIa ($\alpha_{IIb}\beta_3$), Charo *et al.* teach that 7E3 inhibits platelet aggregation, and that Mohle *et al.* teach that platelet aggregation leads to release of VEGF and hence angiogenesis.

Applicants respectfully disagree with this line of argument as well. As discussed above, Max *et al.* do *not* teach a role for $\alpha_v\beta_3$ in proliferative and inflammatory disorders. Moreover, Brooks *et al.*, the true source of the teaching cited by the Examiner, teach only a role for antagonists of $\alpha_v\beta_3$ and actually teach away from the use of anti-GPIIb/IIIa ($\alpha_{IIb}\beta_3$) antibodies for the treatment of these disorders. Thus, no argument can be sustained based on the cited combination of references for the extension of the teachings of Taylor *et al.* to applications in which 7E3 is to be used to antagonize the binding of $\alpha_v\beta_3$. Applicants therefore contend that one of ordinary skill in the art, at the time the invention was made, would not have been motivated to extend the studies of Taylor *et al.* to the treatment of proliferative and/or inflammatory disorders, because there was no evidence at the time implicating both $\alpha_v\beta_3$ and GPIIb/IIIa ($\alpha_{IIb}\beta_3$) in these processes and no evidence that superior results would be obtained through the use of 7E3 relative to LM609, either alone or in combination with 10E5. Furthermore, Applicants respectfully submit that the Examiner's characterization of the prior art, especially as indicated by the choice and application of the prior art references cited in the instant Office Action, suggests that the Examiner is not adhering to the "well-settled principles that the claimed invention must be considered as a whole, multiple cited prior art references must suggest the desirability of being combined, and the references must be viewed without the benefit of hindsight afforded by the disclosure." *In re Paulsen*, 30 F.3d 1475, 1482 (Fed. Cir. 1994).

In light of these findings, Applicants assert that the above-identified references do not render Claims 1-3, 5-11 and 15-17 obvious, and the rejection of these claims should be withdrawn.

CONCLUSION

Based on the foregoing remarks and in light of the amendments, Applicants submit that the present application is in condition for allowance. A Notice of Allowance is therefore respectfully requested.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

Respectfully submitted,

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